Patiromer (VELTASSA™)

National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1]	
Description/Mechanism of Action	Patiromer is a non-absorbed cation exchange polymer of calcium-sorbitol that increases excretion of potassium by binding potassium in the gastrointestinal lumen, thereby reducing serum potassium levels.
Indication(s) Under Review in this document	Patiromer is a potassium binder indicated for the treatment of hyperkalemia. Patiromer should not be used as emergency treatment for life-threatening hyperkalemia due to its delayed onset of action.
Dosage Form(s) Under Review	Patiromer is available in 8.4, 16.8 and 25.2 gram powder packets.
REMS	☐ REMS ☒ No REMS ☒ Post-marketing surveillance (i.e., required pediatric assessments)
Pregnancy Rating	Patiromer is not systemically absorbed. Use of patiromer in pregnant women is not expected to cause harm to the fetus.

Executive Summary[1-16]	
Efficacy	• Patiromer was evaluated in a two-part, single-blind, phase 3 study (OPAL-HK) of patients with chronic kidney disease (CKD) and hyperkalemia (potassium ≥ 5.1 to < 6.5 mmol/L) while receiving a renin-angiotensin-aldosterone system (RAAS) inhibitor. Results of the initial treatment phase in 237 patients reported a reduction in the serum potassium from baseline to week 4 (primary efficacy endpoint) of -1.01±0.03 mmol/L (95% CI -1.07 to -0.95 mmol/L; P<0.001), with 76% of patients achieving target potassium 3.8 to < 5.1 mmol/L (secondary endpoint). The mean daily dose of patiromer in patients with mild hyperkalemia was 12.8 grams, and 21.4 grams in patients with moderate to severe hyperkalemia. Patients with serum potassium ≥ 5.5 mmol/L at baseline and who achieved target potassium at the end of the initial phase while on patiromer and a RAAS inhibitor were eligible for randomization to continue patiromer or to receive placebo during an 8-week withdrawal phase. During the withdrawal phase in these 107 patients, the difference in the median change in serum potassium (primary efficacy endpoint) with placebo (increased) compared to patiromer (no change) was 0.72 mmol/L (95% CI 0.46 to 0.99 mmol/L; P<0.001), with 60% of patients experiencing recurrence of hyperkalemia (potassium ≥ 5.5 mmol/L) (secondary endpoint) on placebo compared to 15% in the patiromer group (between-group difference P<0.001). • Patiromer was also studied in a 52-week, open-label, randomized, dose-finding phase 2 trial (AMETHYST-DN) of 306 patients with CKD and diabetes mellitus (DM) with hyperkalemia (potassium > 5.0 mEq/L) receiving a RAAS inhibitor. Treatment with patiromer reduced the primary efficacy endpoint of mean change in serum potassium at 4 weeks (or prior to dose titration) compared to baseline (reduction of 0.35 to 0.55 mEq/L in patients with mild hyperkalemia, and 0.87 to 0.97 mEq/L in patients in the moderate hyperkalemia, according to dose; P<0.001 for all treatment groups compared to baseline). The mean change in potassium level was maintained from week 4 to week 52 (secondary endpoint). It was

	reported that doses of patiromer were similar at 52 weeks compared to week 4 to 8 of the treatment phase, with a mean daily dose of 19.4 grams for patients with mild hyperkalemia and 27.2 grams in patients with moderate hyperkalemia.
Safety	• There is a **Boxed Warning** for patiromer to administer oral medications either 6 hours before or after receiving patiromer, as patiromer binds to many oral medications that may decrease their absorption and effectiveness. • Patiromer may cause worsening gastrointestinal motility and should be avoided in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, and may also be ineffective in these patients. • Hypomagnesemia may occur due to the binding of patiromer to magnesium in the colon. It is recommended to consider magnesium supplementation if patients experience low magnesium while on therapy with patiromer. • The most common adverse reactions (≥ 2%) occurring with patiromer include constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort and flatulence.
Other Considerations	• Patiromer was also studied in a 4 week trial (PEARL-HF) for prevention of hyperkalemia (off-label use) in patients treated with standard therapy for heart failure (HF) including spironolactone, with lower serum potassium seen with patiromer compared to placebo (difference of -0.45 mEq/L), and fewer patients on patiromer (7.3%) vs. placebo (24.5%) experiencing hyperkalemia. Long-term outcome benefit in this patient population, or for the treatment of hyperkalemia in patients with HF on a RAAS inhibitor, is unknown at this time. • Additional efforts at minimizing hyperkalemia should also be considered (e.g., low potassium diet, evaluation of risk vs. benefit of medications that may contribute to hyperkalemia, consideration of use of non-RAAS inhibitor diuretics as indicated). • The long-term outcomes (e.g., cardiovascular, kidney) with use of patiromer in patients continued on RAAS inhibitor therapy compared to other measures (e.g., adjustment RAAS inhibitor dose or discontinuation) to manage hyperkalemia are unknown at this time.
Projected Place in Therapy	• In a short-term study, patiromer has been shown to reduce serum potassium in patients with CKD and hyperkalemia on a RAAS inhibitor, with a reduction in recurrence of hyperkalemia compared to placebo. Additional long-term outcome data with patiromer are needed to determine its place in therapy compared to other measures to manage hyperkalemia, or in other patient populations. • Patiromer may be considered in patients with persistent or recurrent hyperkalemia while receiving or considering treatment with a RAAS inhibitor, despite adjustments in diet and/or pharmacologic therapy to manage hyperkalemia, where long-term outcome benefit with a RAAS inhibitor is believed to outweigh the risk for hyperkalemia and the cost of addition of a medication to manage hyperkalemia.

Background

Purpose for review	Recent FDA approval. Issues to be determined: ✔ Does the evidence show that patiromer improves long-term outcomes in patients with CKD and hyperkalemia on a RAAS inhibitor? ✔ Determine the most appropriate patients for treatment with patiromer? ✔ What additional safety issues need to be considered with the use of patiromer? ✔ Does patiromer have specific characteristics best managed by the non-formulary process or criteria for use?
Other therapeutic options	Sodium polystyrene sulfonate is a cation exchange resin approved for the treatment of hyperkalemia and is listed on the VA National Formulary

(suspension, oral or rectal).

Efficacy (FDA Approved Indication)[1-4]

Literature Search Summary

A literature search was performed on PubMed/Medline (2011 to January 2016) using the search term patiromer. The search was limited to clinical trials performed in humans and published in the English language. Two randomized trials included in the FDA product labelling, one controlled Phase 3 trial in patients with CKD (OPAL-HK) and one Phase 2 trial in patients with diabetic kidney disease (AMETHYST-DN), are reviewed in detail below.

Review of Efficacy[1-4]

- Patients with CKD and hyperkalemia on a RAAS inhibitor in OPAL-HK treated with patiromer in the 4-week initial treatment phase experienced a reduction in serum potassium of -1.01±0.03 mmol/L (95% CI -1.07 to -0.95 mmol/L; P<0.001), with 76% of patients achieving target potassium 3.8 to < 5.1 mmol/L. The mean daily dose in patients with mild hyperkalemia was 12.8 grams, and 21.4 grams in patients with moderate to severe hyperkalemia. Patients with serum potassium ≥ 5.5 mmol/L at baseline and who achieved target potassium at the end of the initial phase while on patiromer and a RAAS inhibitor were eligible for randomization to continue patiromer or to receive placebo during an 8-week withdrawal phase. During the withdrawal phase in these 107 patients, the difference in the median change in serum potassium (primary efficacy endpoint) with placebo (increased) compared to patiromer (no change) was 0.72 mmol/L (95% CI 0.46 to 0.99 mmol/L; P<0.001), with 60% of patients experiencing recurrence of hyperkalemia (potassium ≥ 5.5 mmol/L) (secondary endpoint) on placebo compared to 15% in the patiromer group (between-group difference P<0.001).[2]
- In AMETHYST-DN, a 52-week, open-label, randomized, dose-finding phase 2 study of 306 patients with CKD and DM with hyperkalemia (potassium > 5.0 mEq/L) receiving a RAAS inhibitor, treatment with patiromer reduced the primary efficacy endpoint of mean change in serum potassium at 4 weeks (or prior to dose titration) compared to baseline (reduction of 0.35 to 0.55 mEq/L in patients with mild hyperkalemia, and 0.87 to 0.97 mEq/L in patients in the moderate hyperkalemia, according to dose; P<0.001 for all treatment groups compared to baseline). The mean change in potassium level was maintained from week 4 to week 52 (secondary endpoint). It was reported that doses of patiromer were similar at 52 weeks compared to week 4 to 8 of the treatment phase, with a mean daily dose of 19.4 grams for patients with mild hyperkalemia and 27.2 grams in patient with moderate hyperkalemia.[3]
- Overall, there is moderate quality of evidence (Refer to Appendix A) for the use of patiromer to reduce serum potassium compared to baseline and vs. placebo in a short-term trial of patients with CKD and hyperkalemia on a RAAS inhibitor.[2]

OPAL-HK[2]

- OPAL-HK was a Phase 3 multicenter, multinational, single-blind, two-phase study in patients with stage 3 or 4 CKD (estimated glomerular filtration rate [eGFR] 15 to < 60 ml/min/1.73m^2 body-surface area), serum potassium 5.1 to < 6.5 mmol/L, and were receiving a stable dose of a RAAS inhibitor for at least 28 days.
- Select main exclusion criteria: potassium related electrocardiographic changes, severe gastrointestinal disorders, uncontrolled or unstable arrhythmias or clinically significant ventricular arrhythmias, recent cardiac surgery, kidney or heart transplantation, acute coronary syndrome, recent (within past 2 months) transient ischemic attack or stroke, systolic blood pressure (SBP) ≥ 180 mm Hg or < 110 mm Hg or diastolic blood pressure (DBP) ≥ 110 mm Hg or < 60 mm Hg. Patients with type 1 DM, emergency treatment for type 2 DM, diabetic gastroparesis, acute HF exacerbation, or New York Heart Association (NYHA) class IV HF were also excluded.
- The two-phase study included a single-blind 4-week initial treatment phase and a randomized, single-blind, placebo-controlled 8-week withdrawal phase. During the initial treatment phase, 243 patients were assigned to either patiromer 4.2 grams twice daily if serum potassium 5.1 to < 5.5 mmol/L (mild hyperkalemia; 92 patients) or 8.4 grams twice daily if serum potassium 5.5 to < 6.5 mmol/L (moderate to severe hyperkalemia; 151 patients). Doses were adjusted to target potassium level, with a mean daily dose of 12.8 grams in patients with mild hyperkalemia and 21.4 grams in patients with moderate to severe hyperkalemia.
- Patients with serum potassium ≥ 5.5 mmol/L at baseline and who achieved target potassium (3.8 to < 5.1 mmol/L) at the end of the initial treatment phase while on patiromer and a RAAS inhibitor were eligible for randomization to continue patiromer (55 patients) or to receive placebo (52 patients) during the 8-week withdrawal phase. In the event of recurrent hyperkalemia, the dose of patiromer was increased (patiromer group) or there was a modification to RAAS inhibitor treatment (placebo group); however, these interventions

were not implemented within the 4-week efficacy endpoint unless potassium was ≥ 5.5 mmol/L.[2] The mean daily dose of patiromer during the withdrawal phase was 21 grams.[1]

- Of the 243 patients enrolled in the treatment phase, 85 of the 92 patients in the mild hyperkalemia treatment group and 134 of the 151 patients in the moderate to severe hyperkalemia treatment group, respectively, completed the initial treatment phase; with 29% and 47% of the withdrawals due to adverse events in the mild and moderate to severe treatment groups, respectively. Of the 219 patients who completed the initial treatment phase, 109 were not eligible for the withdrawal phase, primarily due to not having a baseline potassium ≥ 5.5 mmol/L for the initial treatment phase.
- Select baseline characteristics are included in the table below.

OPAL-HK Select Baseline Characteristics[2]

Characteristic	Initial Treatment Phase	Withdrawal Phase	
	Overall (N=243)	Placebo (N=52)	Patiromer (N=55)
Age	64.2	65.0	65.5
Male	58%	58%	51%
White race	98%	100%	100%
Type 2 DM	57%	63%	62%
Heart failure	42%	42%	49%
Myocardial infarction	25%	27%	33%
Hypertension	97%	96%	98%
Serum potassium (mmol/L)	5.6±0.5	5.9±0.4	5.9±0.6
eGFR ml/min/1.73m^2	35.4±16.2	39.0±20.4	38.6±20.7
RAAS inhibitor use	100%	100%	100%
ACEI	70%	73%	67%
ARB	38%	31%	44%
MRA	9%	8%	7%
Renin inhibitor	1%	0	0
Dual RAAS blockade	17%	12%	18%
Maximum dose	44%	40%	38%
Diuretic (non-RAAS inhibitor)	54%	52%	51%
Thiazide	29%	21%	29%
Loop	32%	38%	29%

- In OPAL-HK, patients with CKD and hyperkalemia (≥ 5.1 and < 6.5 mmol/L) on a RAAS inhibitor treated with patiromer experienced a significant difference in the primary endpoints of reduction in serum potassium after 4 weeks compared to baseline, and compared to placebo in an 8-week withdrawal phase (efficacy endpoint of first serum potassium outside range 3.8 to < 5.5 mmol/L or at 4 weeks) in those with hyperkalemia (≥ 5.5 to < 6.5 mmol/L) at baseline of the initial treatment phase. Results of the primary and secondary endpoints reported in the trial are noted in the table below.

OPAL-HK Initial Treatment and Withdrawal Phase Outcome Results[2]

Outcome	Initial Treatment Phase (N=237[a])		
Primary endpoint	**Mean Change Serum Potassium ± SE (mmol/L)**	**95% CI**	**P**
Overall	-1.01±0.03	-1.07 to -0.95	<0.001
Mild hyperkalemia	-0.65±0.05	-0.74 to -0.55	
Moderate to severe hyperkalemia	-1.23±0.04	-1.31 to -1.16	
Secondary endpoint	**Target Serum Potassium[b] (%)**		
Overall	76	70 to 81	
Mild hyperkalemia	74	65 to 82	
Moderate to severe hyperkalemia	77	70 to 83	
Outcome	**Withdrawal Phase (N=107)**		
Primary endpoint	**Placebo (N=52)**	**Patiromer (N=55)**	
Baseline[c] serum potassium (mmol/L)	4.45	4.49	
Median change serum potassium[d] (mmol/L)	0.72	0	
Between group difference serum potassium	0.72 (95% CI 0.46 to 0.99); P<0.001		
Secondary endpoint	**% (95% CI)**		
≥ 1 serum potassium ≥ 5.5 mmol/L[e]	60 (47 to 74)	15 (6 to 24)	

[a] Patients with ≥ 1 serum potassium at a scheduled visit after day 3
[b] Serum potassium 3.8 to < 5.1 mmol/L
[c] Baseline at randomized withdrawal phase

[d] Comparison of baseline vs. week 4 of the 8 week withdrawal phase
[e] Between group difference P<0.001

- According to an exploratory analysis, 62% of patients in the placebo group required an intervention for management of hyperkalemia compared to 16% of patients receiving patiromer; with discontinuation of the RAAS inhibitor in 56% of patients on placebo and 6% of patients on patiromer at the end of the 8 week withdrawal phase. Pre-specified treatment algorithms for the management of recurrent hyperkalemia were followed during the first and second 4 week periods of the withdrawal phase.
- The OPAL-HK study was funded by the pharmaceutical company Relypsa. The investigators note that the study was designed in collaboration with the sponsor, and the authors had full access to the data which were held by the sponsor.[2]

AMETHYST-DN[3]

- AMETHYST-DN was a Phase 2 multicenter, randomized, open-label, dose-ranging study in 304 patients with type 2 DM, CKD with eGFR 15 to < 60 ml/min/1.73m^2 body-surface area, serum potassium > 5.0 mEq/L and receiving a RAAS inhibitor. Patients with serum potassium > 5.0 to 5.5 mEq/L (mild hyperkalemia) were randomized to patiromer 8.4 grams, 16.8 grams, or 25.2 grams per day (divided twice daily); while patients with serum potassium > 5.5 to < 6.0 mEq/L (moderate hyperkalemia) were treated with patiromer 16.8 grams, 25.2 grams, or 33.6 grams per day (divided twice daily). The primary efficacy endpoint of mean change in serum potassium at 4 weeks (or prior to dose titration) compared to baseline is presented in the table below.

AMETHYST-DN Efficacy Results[3]

Treatment Groups	Mean Change Serum Potassium (mEq/L)[a]	95% CI
Mild hyperkalemia (N=220)		
Patiromer daily dose treatment group		
8.4 grams	-0.35	-0.22 to -0.48
16.8 grams	-0.51	-0.38 to -0.64
25.2 grams	-0.55	-0.42 to -0.68
Moderate hyperkalemia (N=84)		
Patiromer daily dose treatment group		
16.8 grams	-0.87	-0.60 to -1.14
25.2 grams	-0.97	-0.70 to -1.23
33.6 grams	-0.92	-0.67 to -1.17

[a] Primary efficacy endpoint; P<0.001 for all treatment groups vs. baseline

- The mean daily dose of patiromer was as follows: for mild hyperkalemia, 18.5 (SD 7.5) grams/day at week 4, 19.6 (SD 9.3) grams/day at weeks 4 to 8, and 19.4 (SD 9.1) grams/day over the 52 week maintenance phase; for moderate hyperkalemia, 26.9 (SD 8.3) grams/day at week 4, 28.0 (SD 12.4) grams/day at weeks 4 to 8, and 27.2 (SD 10.8) grams/day over the 52 week maintenance phase. It was reported that 83.1% to 92.7% of patients with mild hyperkalemia, and 77.4% to 95.1% of patients with moderate hyperkalemia had target serum potassium levels at each monthly scheduled visit through 52 weeks of treatment.
- Over the 52 weeks of treatment, the most common treatment-related adverse event reported was hypomagnesemia in 7.2% of patients, with mild to moderate constipation (6.3%) being the most common reported gastrointestinal event. Hypokalemia (< 3.5 mEq/L) was reported in 5.6% of patients. Discontinuation of treatment related to an adverse event was reported in 9.2% of patients.

Potential Off-Label Use[5]

- Prevention of hyperkalemia was studied in 105 patients with HF and an indication for a RAAS inhibitor, with a serum potassium 4.3 to 5.1 mEq/L, plus either a history of hyperkalemia requiring discontinuation of a RAAS inhibitor and/or a beta-blocker, or CKD and being treated with an ACEI, ARB, and/or beta-blocker. Patients were randomized to patiromer (30 grams/day) or placebo for 4 weeks, with spironolactone initiated at 25 mg per day and increased to 50 mg per day (at day 15) if serum potassium ≤ 5.1 mEq/L. Baseline serum potassium was 4.69 mEq/L for the patiromer group and 4.65 mEq/L in the placebo group. The primary endpoint of difference in change from baseline in serum potassium with patiromer compared to placebo at 28 days was -0.45 mEq/L (P

< 0.001). Fewer patients on patiromer experienced hyperkalemia (serum potassium > 5.5 mEq/L) compared to placebo (7.3% vs. 24.5%, respectively; P=0.015); with more patients receiving patiromer that were able to increase their dose of spironolactone compared to placebo (91% vs. 74%, respectively; P=0.019). At least one adverse event was reported in 54% of patients on patiromer compared to 31% of patients on placebo. Hypomagnesemia (< 1.8 mg/dL) was reported in 24% of patients receiving patiromer vs. 2.1% of patients in the placebo group. It should be noted that this study did not evaluate patiromer for the treatment of hyperkalemia in patients with HF.[5]

Safety[1,2]

(for more detailed information refer to the product package insert)

	Comments
Contraindications[1]	• History of hypersensitivity reaction to patiromer or any of its components
Warnings/Precautions[1]	• **Boxed Warning: Binding to Other Oral Medications** **Patiromer binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness. Administer other oral medications at least 6 hours before or 6 hours after patiromer. Choose patiromer or the other oral medication if adequate dosing separation is not possible.** • Worsening of gastrointestinal motility: use of patiromer should be avoided in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, as patiromer may be ineffective or may worsen gastrointestinal conditions. • Hypomagnesemia: patiromer binds to magnesium in the colon which could result in hypomagnesemia. Hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with patiromer in clinical trials. It is recommended that magnesium be monitored in patients treated with patiromer, and to consider magnesium supplementation in patients with low serum magnesium levels while receiving treatment with patiromer.

Safety Considerations[1]

- In clinical trials, laboratory abnormalities including hypokalemia (potassium < 3.5 mEq/L) was reported in approximately 4.7% of patients; hypomagnesemia (magnesium < 1.4 mg/dl) was reported in approximately 9% of patients.

Adverse Reactions[1-3]

Common adverse reactions[1,2]	In OPAL-HK, the following adverse events were reported with patiromer in the initial treatment phase: ≥ 1 adverse event (47%), constipation (11%), diarrhea (3%), hypomagnesemia (3%), nausea (3%), anemia (3%), chronic renal failure (3%); and vs. placebo, respectively, in the withdrawal phase: ≥ 1 adverse event (47% vs. 50%), headache (4% vs. 8%), supraventricular extrasystoles (4% vs. 2%), constipation (4% vs. 0), diarrhea (4% vs. 0), nausea (4% vs. 0).[2] The most common adverse drug reactions (≥ 2.0%) reported in the product information include constipation (7.2%), hypomagnesemia (5.3%), diarrhea (4.8%), nausea (2.3%), abdominal discomfort (2.0%) and flatulence (2.0%).[1]
Death/Serious adverse reactions[2,3]	In OPAL-HK, 1% of patients treated with patiromer experienced a serious adverse event (SAE) during the initial treatment phase (i.e., 3 patients reported one of the following events: atrial fibrillation; enterococcal endocarditis; escherichia bacteremia; urinary tract infection; subtherapeutic anticoagulation blood levels; chronic renal failure). None of the SAEs were considered by the investigators to be related to treatment with patiromer. No patients randomized to patiromer in the withdrawal phase experienced an SAE; although, an SAE was reported in 2% of patients randomized to placebo. One death (mesenteric vessel thrombosis) was reported in the placebo group during the withdrawal phase.[2] Over 52 weeks in AMETHYST-DN, SAEs were reported in 14.5% of patients,

	with none of the events thought to be related to treatment with patiromer per the investigators. There were 15 deaths (4.9%), none of which were considered by the study investigators to be related to treatment with patiromer, or by the safety review board to be related to hypokalemia or hyperkalemia. Eleven of the 15 deaths were considered by the safety review board to be related to a cardiovascular cause (7 sudden cardiac death, 4 acute myocardial infarction; with 10 patients having a history of atherosclerotic heart disease, heart failure, or both). Of the 7 patients with sudden cardiac death, it was noted that none of these patients had a serum magnesium level less than 1.58 mg/dl.[3]
Discontinuations due to adverse reactions[1]	Discontinuations due to an adverse event in clinical trials with patiromer included: gastrointestinal adverse reactions (2.7%), including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%) and flatulence (0.5%).

Drug Interactions[1,4,6]

Drug-Drug Interactions[1,4,6]

- **Binding to other oral medications:** According to *in vitro* binding studies, patiromer was found to bind to approximately half of the oral medications tested. As binding of patiromer to other orally administered medications could result in decreased gastrointestinal absorption and reduced efficacy if taken within a short period of time of each other, it is recommended to administer other oral medications at least 6 hours before or 6 hours after patiromer. Data from drug interaction studies in healthy volunteers have become available since the approval of patiromer; the manufacturer reports plans to discuss these results with the FDA.

Risk Evaluation

As of January 27, 2016

	Comments
Sentinel event advisories	• None
Look-alike/sound-alike error potentials	See table below

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Patiromer 8.4, 16.8, 25.2 gram powder packet	None	None	None	Patanol Peramivir
VELTASSA	None	None	None	Valtrex Valturna

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations[1,2,4,7-10]

- Patiromer is not for emergency treatment of hyperkalemia, due to its delayed onset of action. According to the product information, a statistically significant reduction in serum potassium was noted at 7 hours after the first dose and throughout the 48 hour dosing interval in one open-label study evaluating the onset of action of patiromer in patients with CKD and hyperkalemia.[1,4]
- Additional efforts at minimizing hyperkalemia should also be considered:[7]
  - At each visit, patients participating in OPAL-HK were counselled on a low potassium diet ($\leq$ 3 grams potassium intake per day) and to limit intake of high potassium foods (> 250 mg per 100 grams).[2]
  - Review and reduce or discontinue medications that may be contributing to hyperkalemia (e.g., nonsteroidal anti-inflammatory drugs, potassium supplements, potassium-sparing diuretics) and where the risk outweighs the benefit.[7]

  - Overall, only slightly over 50% of patients in OPAL-HK were receiving non-RAAS inhibitor diuretics, which may be appropriate management of hyperkalemia, especially in patients with hypertension or hypervolemia.[2,7]
- Although patiromer has been found to be effective in reducing serum potassium in patients with CKD and hyperkalemia on a RAAS inhibitor, it is unknown whether there is a difference in long-term outcomes (e.g., cardiovascular, kidney) with patiromer compared to other measures (e.g., adjustment RAAS inhibitor dose) to manage hyperkalemia.[2,8]
- Another agent, sodium zirconium cyclosilicate, has been studied for the management of hyperkalemia (clinical trials included patients with CKD, DM, HF, treatment with a RAAS inhibitor)[9,10] and has been submitted to the FDA for review and approval.
- Dosing of patiromer in OPAL-HK and AMETHYST-DN was administered twice daily; however, per the FDA clinical pharmacology review, it was felt that once daily dosing would be appropriate for efficacy as well as in order to facilitate the recommendations for a 6 hour dosing interval to avoid potential drug interactions.[1-4]
- It is recommended that patiromer be stored in the refrigerator at 36° to 46°F (2° to 8°C), and to avoid exposure to heat > 104°F (> 40°C). If patiromer is removed from the refrigerator and stored at room temperature, it should be used within 3 months (but not past the manufacturer expiration date).[1]

Dosing and Administration[1]

- Patiromer should not be taken in dry form. Each dose of patiromer should be prepared immediately prior to administration as follows:
  - Step 1: Add approximately 1 ounce (30 ml) water to an empty glass or cup
  - Step 2: Empty the entire packet(s) contents into the glass or cup
  - Step 3: Stir the mixture thoroughly
  - Step 4: Add an additional 2 ounces (60 ml) of water to the glass or cup that contains the mixture
  - Step 5: Stir the mixture thoroughly (the powder will not dissolve and will appear cloudy)
  - Step 6: Immediately drink the mixture. If some powder remains in the glass, add more water, stir and drink immediately. Repeat as necessary to ensure the entire dose is administered.
- The initial dose of patiromer is 8.4 grams once daily. Serum potassium should be monitored, with the dose of patiromer adjusted based on the potassium level and treatment goal. The dose of patiromer may be increased or decreased, up to a maximum of 25.2 grams once daily, to achieve the desired serum potassium. The dose may be titrated according to serum potassium at intervals of one week or more, by increments of 8.4 grams.
- Patiromer should be administered with food. It should be mixed with water only. Patiromer should not be heated, microwaved, or added to heated foods or liquids.

Special Populations (Adults)[1]

	Comments
Elderly	• In clinical trials with patiromer, 59.8% of the patients were ≥ 65 years of age, with 19.8% ≥ 75 years of age. No differences in effectiveness were noted between older and younger patients. Patients ≥ 65 years of age reported more gastrointestinal adverse reactions compared to younger patients.
Pregnancy	• Patiromer is not systemically absorbed. Use of patiromer in pregnant women is not expected to cause harm to the fetus.
Lactation	• Patiromer is not systemically absorbed, so breastfeeding is not expected to increase risk to the infant.
Renal Impairment	• The majority of patients (93%) enrolled in the clinical trials with patiromer had CKD. No dosage adjustment is needed in patients with renal impairment.
Hepatic Impairment	• No data identified.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy[1-7,11-18]

- Treatment with a RAAS inhibitor is generally well-tolerated, with hyperkalemia occurring infrequently in patients without risk factors that may contribute to elevated serum potassium, such as CKD, DM, use of potassium supplements or potassium-sparing diuretics.[7,11] In one study that included patients with vascular disease or high-risk DM, 3.3% of patients treated with an ACEI and 3.36% of patients who received an ARB were reported to have a potassium level > 5.5 mmol/L.[12] In another study evaluating changes in serum potassium in patients with renal insufficiency receiving a RAAS inhibitor, patients with moderate kidney dysfunction (GFR < 60 ml/min/1.73m^2) experienced a mean increase in serum potassium of 0.28 mEq/L above baseline (4.6 mEq/L) with an ACEI, and a mean increase of 0.12 mEq/L with an ARB.[13]
- The risk vs. benefit of continuing a RAAS inhibitor in the presence of hyperkalemia with initiation of treatment for hyperkalemia, compared to adjusting therapy with the RAAS inhibitor to manage hyperkalemia, should be taken into consideration. The long-term outcome benefits of patiromer in this setting have not been established. Therefore, the risk vs. outcome benefit of continuing the RAAS inhibitor (e.g., clinical practice guidelines recommend [Grade 1B] treatment with an ACEI or ARB in patients with CKD with albuminuria [urine albumin excretion > 300 mg/24 hours];[14] and in patients with HF with reduced ejection fraction, an ACEI [or ARB if ACEI intolerant] and a mineralocorticoid receptor antagonist are recommended [Class I Recommendation; Level of Evidence: A][15]) in the presence of hyperkalemia needs to be taken into consideration. It is noted that approximately 42% of patients had concomitant heart failure that were enrolled in the clinical trial of patiromer in patients with chronic kidney disease.[2] Patiromer has not been specifically studied in patients with heart failure with reduced ejection fraction (without chronic kidney disease) for treatment of hyperkalemia on a RAAS inhibitor.
- If it is determined that the benefit of treatment with a RAAS inhibitor warrants continued therapy, several measures may be implemented to potentially reduce serum potassium (e.g., counselling on a low potassium diet; review of medications including NSAIDs, potassium-sparing diuretics, potassium or herbal supplements for adjustment or discontinuation; consideration of loop or thiazide diuretic therapy, as indicated).[6,16] Sodium polystyrene sulfonate, a cation exchange resin that exchanges sodium for potassium in the colon, has also been used to manage hyperkalemia, either orally or as an enema. The potential for edema as a result of sodium retention (each 15 gram dose of sodium polystyrene sulfonate contains approximately 1.5 grams sodium, with approximately 33% efficiency of sodium for potassium exchange, estimating approximately 500 mg sodium released into the body[17]) may be a consideration in some patients at risk for or from sodium or fluid overload. Concerns of intestinal necrosis, which may be fatal, with sodium polystyrene sulfonate resulted in changes to the product labeling to warn against use in patients at increased risk of developing constipation or impaction (including postoperative patients) and to caution against use of sodium polystyrene sulfonate with additional sorbitol, as concomitant use has been associated with the cases of intestinal necrosis.[18]
- Results from one Phase 3 clinical trial of patiromer in patients with CKD and hyperkalemia on a RAAS inhibitor demonstrated a statistically significant reduction from baseline in serum potassium (-1.01$\pm$0.03 mmol/L) at 4 weeks with treatment; with 76% of patients achieving target potassium 3.8 to < 5.1 mmol/L. During an 8 week withdrawal phase of the same study in patients with serum potassium $\geq$ 5.5 mmol/L at baseline and who achieved target potassium at the end of the initial treatment phase while on patiromer and a RAAS inhibitor, there was a statistically significant difference in serum potassium with patiromer (no change) compared to placebo (0.72 mmol/L); with 60% of patients experiencing recurrence of hyperkalemia (potassium $\geq$ 5.5 mmol/L) on placebo compared to 15% in the patiromer group.[2] Results from one Phase 2 study in patients with CKD and DM with hyperkalemia receiving a RAAS inhibitor showed that the mean change in potassium level was maintained throughout the 52 week trial duration.[3] It is noted, however, that the long-term outcomes (e.g., cardiovascular, kidney) with patiromer compared to other measures (e.g., adjustment of RAAS inhibitor dose) to manage hyperkalemia in patients with CKD on a RAAS inhibitor are unknown at this time. In addition, the long-term outcome benefit of patiromer in patients with HF (with or without CKD) on a RAAS inhibitor for management of hyperkalemia has not been established at this time.
- The most common adverse reactions with patiromer include gastrointestinal complaints and hypomagnesemia.[1] There is a **Boxed Warning** to administer other oral medications at least 6 hours before or 6 hours after patiromer, due to the potential binding of patiromer to other orally administered medications that could result in decreased gastrointestinal absorption and reduced efficacy if taken within a short period of time of each other, and to choose patiromer or the other oral medication if adequate dosing separation is not possible.[1] Recent drug interaction studies in healthy volunteers have been conducted by the manufacturer, with plans to discuss these

data with the FDA.[6] The FDA has also recommended that potential drug interaction studies be undertaken for sodium polystyrene sulfonate, and that there be a separation of 6 hours between sodium polystyrene sulfonate and other oral medications.[18]

- Treatment with patiromer may be considered in patients with hyperkalemia while receiving or considering treatment with a RAAS inhibitor: after adjustment of the RAAS inhibitor; consideration of the risk vs. benefit of RAAS inhibitor therapy; despite initiation of non-RAAS inhibitor diuretic therapy (e.g., loop or thiazide diuretics), as indicated; and adjustment or discontinuation of other medications or herbal treatments that may contribute to hyperkalemia. The risk vs. benefit of initiating treatment with patiromer in order to manage hyperkalemia, a potential adverse effect of continuing therapy with a RAAS inhibitor, needs to be taken into consideration given the lack of long-term outcome data with the use of patiromer in this patient population. If it is determined to initiate chronic therapy for hyperkalemia, a trial of sodium polystyrene sulfonate should be considered, where appropriate.
- Overall, there is moderate quality of evidence (Refer to Appendix A) for the use of patiromer to reduce serum potassium compared to baseline and vs. placebo in a short-term trial of patients with CKD and hyperkalemia on a RAAS inhibitor.

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Contact person: Elaine M. Furmaga, PharmD; National PBM Clinical Pharmacy Program Manager

Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.